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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/782,077	02/14/2001	Jonathan S. Stamler	1661 - CIP	9791

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EXAMINER
PAK, JOHN D

ART UNIT	PAPER NUMBER
1616	

DATE MAILED: 08/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N . 09/782,077	Applicant(s) STAMLER, JONATHAN S.
	Examiner JOHN D PAK	Art Unit 1616

-- The MAILING DATE of this c mmunicati n appears n the c ver sheet with th c rrespondence address --

Period f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-11 and 13-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,7-11 and 13-16* is/are rejected.

7)☒ Claim(s) *4 and 5* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Claims 1-5, 7-11 and 13-16 are pending in this application.

Claims 1-3, 7-9 and 14-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the specific substances delivered as gases that have been identified in the specification (e.g., ethyl nitrite, NOH, NO-halogen, N_2O_3), does not reasonably provide enablement for other gases that have not been specifically disclosed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The nature of the invention here is in treating pulmonary disorders associated with depletion of s-nitrosoglutathione pool in the lung, depletion of glutathione pool in the lung or production of reactive oxygen species by delivering into the lung, as a gas, an agent that counters such mechanisms. In effect, without a specific recitation of the identity of the agent(s), this is a circular claim, not unlike "method of curing AIDS by administering an agent that kills the virus that causes AIDS." It is the identification of the effective therapeutic agent that is the invention, particularly when one considers the diverse pulmonary disorders that are encompassed by the claims: asthma (not claims 14-15), hypoxemia, cystic fibrosis, lung infection, lung injury, pulmonary hypertension, adult respiratory distress syndromes, pneumonia, pulmonary fibrosis, interstitial lung diseases.

The state of the prior art is such that there is no one uniform substance that is known to effectively treat all such diverse disorders. Applicant's specification teaches that the inventive agents are those agents, when delivered as gases, that cause

repletion or increase of s-nitroglutathione pool in the lung or protect against toxicity where glutathione is depleted in the lung or where reactive oxygen species are increased in the lung. But just what exactly are the metes and bounds of such agents? How does one skilled in the art figure out what they are?

Applicant's specification (pp. 8-10) discloses some examples:

- substances that have an NO group but such that the NO group is bound so it does not form NO_2, NO, N_2O_3, N_2O_4, $OONO^-$, OONO* and any products of interaction with NO or NO_2
- ethyl nitrite, methyl nitrite, trifluoronitrosomethane
- NOX or XNO, where X is H or halogen, or NOX or XNO generating agents
- RSO_2NO, SOClONO, $SO(ONO)_2$, $RSNO_2$, nitrosourea.
- N_2O_3, H_2S
- working examples with NOCl, NOCN, methylnitrososulfinate, thionitrosochloronitrite, thionyldinitrite, methylthionitrite, ethylnitrite, H_2S and HNO.

The point of this ground of rejection is that besides the specific examples disclosed in the specification, one skilled in the art would be faced with undue experimentation in determining other gases that are within the scope of the invention.

While the relative skill of those in the art is quite high given the therapeutic medicine for a patient that is involved here, the unpredictability of the art is also quite high. The claimed invention is directed to treating myriad pulmonary disorders,

including asthma (not claims 14-15), hypoxemia, cystic fibrosis, lung infection, lung injury, pulmonary hypertension, adult respiratory distress syndromes, pneumonia, pulmonary fibrosis, interstitial lung diseases. These diseases have different and distinct etiologies and are not known to be treated with the same protocol. Further, the ultimate end effect of most gases, let alone many gases that are related to (or have) NO group, is not predictable in the absence of further experimentation. NO can generate toxic free radicals and oxides of nitrogen that can make matters worse for patients of said pulmonary disorders. Reactive nitrogen species in lung injury and fibrosis are a problem (Chemical Abstracts 137:273028, 138:120791; see also 136:245117).

Therefore, there is a concern that even the substances noted above (p. 3) may contribute to generation of the harmful nitrogen species, which goes to show just how complicated it is to obtain the effective therapeutic end result applicant claims with gases that have not been specifically identified in the specification. One skilled in the art would have to resort to taking a patient with pulmonary disorders and experimenting with various gases to see if the gases would replete GNSO pool in the lung or provide protective effect. There is not a lot of room for experimental error or ineffectiveness in treating patients with pulmonary conditions such as pulmonary hypertension in infants, lung injury, pneumonia, cystic fibrosis and severe asthma.

As a result, based on the totality of factors considered above, one skilled in the art would be faced with an amount of experimentation that is undue in having to determine suitable gases that would have therapeutic effectiveness, as claimed. Consequently, the claims must be rejected as lacking in adequate enabling support.

The **Examiner suggests** applicant limiting the claims to those specific compounds that have been identified as suitable agents for administration as gases (but see below for discussion on excluding H_2S).

Claims 10-11 and 13-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for specific substances delivered as gases that have been identified in the specification (e.g., ethyl nitrite, NOH, NO-halogen, N_2O_3), does not reasonably provide enablement for H_2S in the absence of further limiting features. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The basis for this ground of rejection is in the scope of the claims wherein H_2S is administered to patients with pulmonary disorders. But note, H_2S is an asphyxiant gas. It was already shown by the cited references in the previous Office Actions that administration of H_2S to asthmatic patients would be detrimental. Clearly, from the cited references on page 3 of Paper No. 6 (10/31/02), one skilled in the art would not administer H_2S to asthmatics. Furthermore, there is additional contravening evidence with respect to broader types of pulmonary disorders and H_2S. Toxcenter accession no. 2002:618658 discloses that hydrogen sulfide is an asphyxiant gas, which at high doses has the same effect as high doses of cyanide; 100-150 ppm inhalation results in irritation; 900 ppm causes serious systemic effects in less than 30 minutes and death in

1 hour; is known to cause pulmonary edema; and earliest toxic response in occupation settings is 10.5 ppm.

Against this state of the art about an asphyxiant gas, applicant would administer the same asphyxiant H_2S gas to the bronchially challenged asthmatics and other patients with pulmonary disorders. Note, claims 10-11 are open to 100 ppm H_2S, and claims 14-16 are without specific limits as to concentration of H_2S. One skilled in the art would be faced with undue experimentation in obtaining the claimed therapeutic results. Applicant's specification Example X is noted in this regard, but the claims are nowhere commensurate in scope with the tightly controlled treatment protocol that produced such result.

Applicant has submitted several documents on threshold limit value and exposure acceptability of H_2S, but applicant fails to take into account the fact that such values are not for already-challenged individuals such as those with asthma, lung injury, cystic fibrosis, hypoxemia, pulmonary hypertension, ARDS or pneumonia. The Examiner has provided sufficient evidence that H_2S is an asphyxiant gas that is not expected to be effective in the absence of further limitations. Applicant argues that some drugs are useful even if they have some harmful effect to some members of the patient pool – however, to date, applicant's evidence has been found insufficient to outweigh the evidence of harmful effect of an asphyxiant gas to patients with pulmonary disorders. Treatment of those pulmonary-challenged patients must be more specifically defined so that the asserted beneficial effect of a known asphyxiant gas can be

practiced without resorting to undue experimentation as to concentration, duration, and other protocol measures.

Claims 4-5 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JOHN D PAK whose telephone number is (703)308-4538. The examiner can normally be reached on Monday to Friday from 8 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page, can be reached on (703) 308-2927. The fax phone number for the organization where this application or proceeding is assigned is (703)308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703)308-1235.

JOHN PAK
PRIMARY EXAMINER
GROUP 1600